

Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 3-9, 11-20, 23, 24, 40-48 are pending in the application, with claim 40 being the only independent claim. Claims 1, 2, 10, 21, 22, and 25-39 have been previously canceled without prejudice to or disclaimer of the subject matter therein, with claims 25-39 being drawn to non-elected invention. New claims 45-48 are added, and claims 4, 11, 13, 14, 40, 42 and 44 are amended. Support for the new claims and the claim amendments appears throughout the specification. In particular, support for new claims 45-47, and the amendments to claims 42 and 44, is found, for example, in the specification at paragraph [0080]. Support for new claim 48 is found, for example, in the specification at paragraph [0089]. Support for the amendments to claims 11 and 40 is found, for example, in the specification at paragraphs [0076] and [0080]. Support for the amendment to claim 14 is found, for example, in the specification at paragraph [0078]. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Claim Objections

Claims 40 has been objected to because the Examiner alleges the claim should be amended for clarity to recite -- device, the method comprising --. Claim 40 has also been objected to because the Examiner alleges the claim should be amended in the preamble

for clarity to recite --wherein the device comprises a lysis reactor, a neutralizing reactor and a clarification reactor fluidly connected to one another--. To expedite prosecution, and without acquiescing to the objection, Applicants have amended the preamble of claim 40 to recite "wherein the device comprises a lysis reactor, a neutralizing reactor and a clarification reactor fluidly connected to one another, the method comprising," as suggested by the Examiner. Applicants therefore respectfully request that these objections of claim 40 be withdrawn.

Claim 40 has also been objected to because the Examiner alleges each of steps "c) neutralizing, in a neutralization reactor" and "d) separating, in a clarification reactor" improperly suggest the hand of man. *See* Office Action, page 2. The Examiner suggests that claim 14 should be amended for clarity as proposed on page 3 of the Office Action. To expedite prosecution, and without acquiescing to the objection, Applicants have amended claim 40 to recite "c) transporting the lysed cell solution via the neutralization reactor wherein the lysed cell solution is mixed with a neutralization solution to produce a mixture comprising a lysate and a precipitate comprising cellular debris and impurities, and wherein the lysate contains the biomolecule of interest; . . . d) introducing the mixture comprising the precipitate and the lysate into the clarification reactor wherein the lysate containing the biomolecule of interest is separated from the precipitate, wherein the mixture comprising the precipitate and the lysate is allowed to flow through the clarification reactor, and wherein the clarification reactor contains a retention layer that functions to retain the precipitate but allow the lysate to flow from the clarification reactor." This claim amendment incorporates several of the Examiner's suggestions.

Applicants believe appropriate correction has been made, and respectfully request that this objection of claim 40 be withdrawn.

Claim 40 has also been objected to because the Examiner asserts that the claim mentions a device in the preamble but does not mention tubing as the fluid connection between the reactors and does not mention what is driving the claimed "defined ratio of flow rates" of the cell suspension and lysis solution introduced into the lysis reactor. The Examiner asserts that the claim should be further amended in the preamble for clarity to recite that the reactors are fluidly connected to one another "by a tubing system and wherein transportation between the reactors is mediated by pressure or pumps." See Office Action, page 3. Applicants respectfully disagree. Applicants submit that the claim does not require a recitation of a particular means for achieving fluidly connecting the reactors (e.g., tubing) or a recitation of a particular means for driving a flow rate (e.g., pressure or pumps) in order to be sufficiently clear. Such details are not essential to practicing the claimed method and do not render the claim as not enabling. *See MPEP 2172.01*. It is sufficient to state, as recited in amended claim 40, that the reactors are fluidly connected and there are flows of the cell suspension and the lysis solution into the reactor. Indeed, dependent claim 14 has been amended to specify an embodiment of such nonessential aspects, and recites that the flows "are transported at a defined ratio of flow rates, the flow rates being regulated by pressure or pumps." Further, to expedite prosecution, and without acquiescing to the objection, Applicants have amended claim 40 to delete the language "defined ratio of flow rates". Applicants respectfully request that this objection of claim 40 be withdrawn.

Claim 40 has also been objected to because the Examiner alleges that the recitation that the cell suspension is a fermentation broth lacks a recitation of where the fermentation broth originates. To expedite prosecution, and without acquiescing to the objection, Applicants have amended step a) of claim 40 to recite "providing a cell suspension of host cells that have been cultivated to produce the biomolecule of interest, wherein the cell suspension is a fermentation broth within which the host cells were cultivated or a re-suspension of the cultivated host cells that were harvested from the fermentation broth." Thus, amended claim 40 clarifies that the fermentation broth is a broth within which the host cells were cultivated. Applicants believe appropriate correction has been made, and respectfully request that this objection of claim 40 be withdrawn.

Claim 4 was objected to because the Examiner alleges that the claim should be amended to recite --the particulate material consists of glass beads-- for clearer antecedent basis. To expedite prosecution, and without acquiescing to the objection, claim 4 has been amended to recite "the particulate material of the retention layer consists of glass beads." Applicants therefore respectfully request that the objection of claim 4 be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 2, 3, 5, 9, 11-20, 23, 24, 40, 41, and 44 were rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent Publication No. 2006/0106208 to Nochumson ("Nochumson"). Claim 2 has been cancelled, rendering its rejection moot. The Examiner alleges that Nochumson discloses a particulate material in the lysis reactor as

being a precipitate of salt and detergent. See Office Action, page 10. Examiner is broadly construing "particulate material" to include solid particles that are not dissolved in solvent. Claim 40 has been amended to specify that "the lysis reactor contains filling elements made of glass, plastic, stainless steel or fibrous material," and that "the flow of the cell suspension and the flow of the lysis solution are homogenously mixed as a result of flowing through the filling elements in the lysis reactor."

Nochumson does not disclose a lysis reactor that *contains filling elements* made of glass, plastic, stainless steel or fibrous material, with the flow of the cell suspension and the flow of the lysis solution being homogenously mixed as a result of flowing through the filling elements, as claimed. Rather, Nochumson discloses an alkaline lysis process in which the means for providing mixing of the cells and the lysis solution for cell lysis involves an in-line static mixer and a lysis coil. See Figure 1 and paragraph [0055] of Nochumson. The process of Nochumson lacks a lysis reactor that *contains filling elements*, which allows for homogenously mixing of the cell suspension and the lysis solution. Consequently, Nochumson does not anticipate independent claim 40, or claims 3, 5, 9, 11-20, 23, 24, 40, 41, and 44 which depend there from. Therefore, Applicants respectfully request that the rejections of these claims based on Nochumson be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 2, 3, 5, 9, 12-20, 23, 24, 40 and 41 were rejected under 35 U.S.C. § 103(a) as being unpatentable over the Nochumson reference in view of U.S. Patent No. 6,381,967 to Craig ("Craig"). Claims 2-9, 11-20, 23, 24, 40, 41, 43 and 44 were also

rejected under 35 U.S.C. § 103(a) as being unpatentable over the Nochumson reference in view of U.S. Patent No. 5,561,064 to Marquet et al. ("Marquet") or U.S. Patent No. 5,783,686 to Gonzalez et al ("Gonzalez"). Claim 2 has been cancelled, rendering its rejection moot.

Claim 40 has been amended to recite that "the lysis reactor contains filling elements made of glass, plastic, stainless steel or fibrous material, wherein the flow of the cell suspension and the flow of the lysis solution are homogenously mixed as a result of flowing through the filling elements in the lysis reactor so that irreversible denaturation of the biomolecule of interest is avoided and the cultivated host cells are disintegrated by alkaline lysis in the absence of shear forces in the lysis reactor." It was surprisingly found that incorporating filling elements *in the lysis reactor* could achieve sufficient mixing and contacting for alkaline lysis. *See* paragraph [0046] of the present application. Further, the mixing is achieved while avoiding disadvantageous shear forces. Other lysis methods, such as those using simple tubing, may avoid shear forces, but do not achieve homogenous mixing. Homogenous mixing ensures local pH-extremes are avoided which irreversibly denature the plasmid. *See* paragraphs [0017], [0026] and [0076] of the present application.

As noted above, Nochumson does not disclose a lysis reactor that *contains filling elements* made of glass, plastic, stainless steel or fibrous material, as claimed.

The Examiner asserts that the art is replete with methods for clarification in which *lysates* are filtered through sinter plates or glass beads and cites Marquet and Gonzalez. *See* Office Action, pages 9 and 10. However, Craig, Marquet, and Gonzalez also do not disclose a *lysis* reactor that contains sinter plates or glass beads, or other

filling elements. Marquet describes that lysis may be carried out in a dilute base or a base and detergent, or alternatively, lysis may be carried out by mechanical breakage using a French Press or a micro fluidizer. *See* col. 7, line 51 - col. 8, line 4 of Marquet. Marquet provides no description of alkaline lysis in the presence of filling elements wherein lysis is carried out in the absence of shear forces. Gonzalez describes lysis by adding a solution of NaOH to the cells, and is also silent with regard to lysis in the presence of filling elements. *See* Col. 5., lines 10-12. Craig does not cure the deficiencies of Marquet and Gonzalez. Craig is directed to cryogenic freezing of liquids and makes no reference to cell lysis.

The Examiner points out that KSR forecloses the argument that specific teaching, suggestion or motivation is required to support a finding obviousness. Notwithstanding, the Examiner has not shown a reason to combine the teachings of a clarification method using filling elements with an alkaline lysis method to arrive at a lysis reactor that "*contains filling elements*," as claimed. None of the cited references teach or suggest the usefulness of employing a lysis reactor that contains filling elements. Accordingly, the Examiner has not shown the claimed invention is obvious under KSR. Further, even assuming, *arguendo*, there exists a motivation to combine the filter systems of Marquet and Gonzalez with the process of Nochumson, none of the cited references teach or suggest that the cell suspension and the lysis solution can be "homogenously mixed as a result of flowing through the filling elements in the lysis reactor so that irreversible denaturation of the biomolecule of interest is avoided and the cultivated host cells are disintegrated by alkaline lysis in the absence of shear forces in the lysis reactor," as

provided by claim 40. In sum, the Examiner has not set forth a *prima facie* case of obviousness.

Claims 2-9, 11-20, 23, 24, 40-42, 43 and 44 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent Publication No. 2006/0106208 to Nochumson ("Nochumson") in view of U.S. Patent No. 5,846,764 to Demaggio *et al.* ("Demaggio") or U.S. Patent No. 6,617,105 to Rudi *et al.* ("Rudi"). Claim 2 has been cancelled, rendering its rejection moot. The Examiner alleges that Demaggio *et al.* (U.S. Patent No. 5,846,764), and Rudi *et al.* (U.S. Patent No. 6,617,105) disclose glass beads used in cell lysis. However, the use of the glass beads in these references is for *mechanical* lysis, in which shear forces are used to disintegrate cells. Neither Demaggio or Rudi teach or suggest homogenously mixing of the cell suspension and the lysis solution in a manner in which cultivated host cells are disintegrated by alkaline lysis *in the absence of shear forces* in the lysis reactor, as claimed.

Accordingly, independent claim 40, and claims 3-9, 11-20, 23, 24, and 40-44, which depend from claim 40, as well as new claims 45-48, which also depend from claim 40, are patentable at least for the reasons noted above. Further, with respect to new dependent claim 46, none of the cited references disclose the lysis reactor being essentially completely filled with particulate material. While the Examiner alleges that Demaggio or Rudi disclose glass beads used in cell lysis, the glass beads used in mechanical lysis must move in a vortex-type movement in the biological sample and do not essentially completely fill a lysis reactor.

Applicants respectfully request that the rejections be withdrawn and the claims allowed.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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